REMARKS

In an Advisory Action mailed April 23, 3008, the Examiner refused to enter an amendment that was timely filed in response to a final office action. According to the Examiner, the amendments raise new issues that would require further consideration and/or search, raise new issues of matter, and are not deemed to place the application in better form for appeal or condition for allowance.

In the Advisory Action, the Examiner notes the need to clarify new claim 26 with regards what is operably linked to one or more expression control sequences. By this amendment, Applicants have reworded claim 26 to more clearly define the invention.

In a final office action mailed October 30, 2007, claims 1-9, 11-14, 24 and 25 have been rejected. In response, Applicants provide the herein amendments and remarks. Claim 1 has been cancelled, new claim 26 has been added and claims 2-5, 9, 11 and 14 have been amended. Claims 2-9, 11-14 and 24-26 are being considered. Claims 10, 15-17 and 19-23 remain withdrawn. Reconsideration is respectfully requested.

New claim 26 has been added due to extensive revisions of claim 1, and finds support in original claim 1. Claims 2-5, 9, 11 and 14 have been amended to change claim dependency from claim 1 to claim 26. No new matter has been added.

Rejections Under §112

In the office action, claims 1-9, 11-14 and 24-25 have been rejected under §112, second paragraph, as being indefinite. In particular, the Examiner contends that the recitation of "provided in the genome thereof, with the coding sequence of at least one restoring factor" in claim 1 is unclear.

In response, Applicants have cancelled claim 1 and added new claim 26 which more clearly recites the claim limitation. Claim 26 reads: "wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells."

Applicants assert that new claim 26 clearly recites that the adenovirus's genome comprises the restoring factor sequence. Accordingly, Applicants respectfully request that the rejection under §112, second paragraph be reconsidered and withdrawn.

Rejections Under §102

Claims 1-2, 9 and 24-25 continue to be rejected under §102(b) as allegedly being anticipated by Fueyo et al. as evidenced by Nevins. According to the Examiner, Fueyo et al.

teach an adenovirus having the same structure as the claimed adenovirus, and therefore, "accelerated cell lysis" or "faster release of virus progeny" (as claimed) would be instrinsic to the recombinant adenovirus taught by Fueyo et al.

In response, claim 1 has been cancelled and new claim 26 has been added. New claim 26 recites "wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells."

Fueyo et al. disclose an adenovirus with a 24 base pair deletion in the E1A region as the only genomic alteration when compared to a wild type adenovirus. Fueyo et al. do not disclose an adenovirus having a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells (as recited in new claim 26). Accordingly, Fueyo et al does not anticipate the claimed invention.

Furthermore, the 24 base pair E1A deletion disclosed in Fueyo et al. is not able to bind Rb (see abstract of Fueyo et al) and the expression of this mutant E1A protein will not induce the release of E2F from existing Rb-E2F complexes. The lack of activation of E2F will not result in activation of the p53 pathway, as is evidenced in Nevins. Thus, the mutant E1A as disclosed by Fueyo et al. is unable to restore the p53 apoptosis pathway, simply because the protein cannot bind Rb.

Accordingly, in light of the above, Applicants respectfully request that the Examiner reconsider and withdraw the §102(b) rejection based on Fueyo et al. as evidenced by Nevins.

Rejections Under §103

Claims 1-8, 11-14 and 24 continue to be rejected under §103(a) as being unpatentable over Lin et al. in view of Chang et al. According to the Examiner, Lin et al. and Chang et al. collectively teach all of the structural limitations of the claimed adenovirus. The Examiner recognizes that Lin and Chang do not teach the specific controls recited in the claims. However, the Examiner asserts that the type of controls recited in the claims are obvious and not an important structural limitation. Therefore, the claims remain rejected as stated above.

In response, Applicants have cancelled claim 1 and added new claim 26. New claim 26 recites "wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells." Neither Lin et al. nor Chang et al. disclose the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells.

In order to establish *prima facie* obviousness rejection under §103, one of the criteria to be met is that upon combining the references, all of the claim limitations must be taught.

Applicants have explained the importance of the adenovirus genome comprising a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in the target cells. See above.

Upon combining the teachings of Lin et al. and Chang et al., all of the claim limitations re not met. Therefore, Applicants respectfully request that the rejection under §103 based on Lin et al. in view of Chang et al. be reconsidered and withdrawn.

Furthermore, Applicants respectfully submit that the Examiner has used hindsight in combining Lin et al. and Chang et al. At the time of filing the present application, the skilled person had no reasonable expectation of success for such a combination.

The interest in replication competent adenoviruses in the targeting of tumors comes from the fact that such vectors have a better penetration than typical replication defective adenoviruses. It is thought that these viruses are more effective because they release from the cell to infect neighboring cells. This in situ amplification effect is essential; and inherent in the use of replication competent viruses for this purpose (See, Hermiston and Kuhn, first paragraph

of the introduction on page 1022, attached hereto). This review was published shortly after the effective date of the application.

A skilled person considering the development of a novel replication competent virus for this purpose would thus never incorporate the coding region for a protein that would attenuate virus replication. In the mind set of the skilled person, such a protein negates the utility of the replication competent virus. The skilled person would therefore not select such a coding region for incorporation into a replication competent adenovirus with the expectation that such a coding region would increase the effectiveness of the replication competent virus.

This lack of reasonable expectation of success is clearly illustrated on page 1026 of Hermiston and Kuhn, right hand column, which states:

"A second disadvantage of using oncogene inhibitors or tumor supressors to arm replication competent oncolytic viruses is that the action of the inhibitors and supressors, while toxic to the target tumor cell, is also likely to attenuate virus replication."

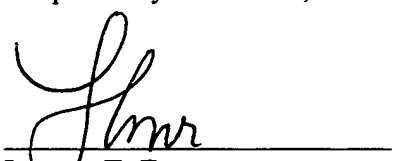
Furthermore, Applicants respectfully remind the Examiner of his own "expectation of success" expressed in the Office Action dated July 31, 2006. Under §112 on page 6 of the office action, the Examiner interpreted the art and concluded that p53 dependent apoptosis is prevented through the action of the E1B proteins. The Examiner came to the same conclusion as the skilled person at the time of the invention, i.e. that the combination of Lin and Chang would not work.

It is respectfully submitted that the combination of Lin and Chang is only possible using the knowledge of the invention, i.e. hindsight. In fact, it was the present inventors that discovered the surprising effect of the replication competent viruses of the invention. There was no indication of this effect in the art available at the time the application was filed. The available art actually teaches away from the present invention. The negative aspects associated with the viruses of the invention prevented the skilled person from having any reasonable expectation of success.

Again, in light of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw the §103 rejections.

It is now believed that the application is in condition for allowance. If the Examiner believes a telephone discussion would be beneficial to resolve any outstanding issue, she is invited to contact the undersigned without hesitation.

Respectfully submitted,



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